COMMENTS ON THE DRAFT DOCUMENT ENTITLED

"HEALTH EFFECTS OF PASSIVE SMOKING: ASSESSMENT OF LUNG CANCER IN ADULTS AND RESPIRATORY DISORDERS IN CHILDREN"

Comments prepared by:

Ronald D. Hood, Ph.D., Raphael J. Witorsch, Ph.D.,
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Dr. Ronald Hood has been a Professor of Biology in the Cell, Molecular, and Developmental Biology Section, Department of Biology, The University of Alabama, since 1978. He holds a concurrent appointment as Adjunct Professor of Environmental Health Sciences in the School of Public Health at the University of Alabama at Birmingham. He is also the Principal Associate in R. D. Hood and Associates, Toxicology Consultants. Since 1978, he has acted as a professional consultant in the areas of environmental, developmental, and reproductive toxicology for a number of industrial clients and law firms, and for numerous federal agencies, including the EPA, the Veterans Administration, the Congressional Office of Technology Assessment, and the National Institute of Environmental Health Sciences. He is currently a consultant to the EPA's Science Advisory Board (Halogenated Organics Subcommittee of the Environmental Health Committee) and to the National Institute of Environmental Health Sciences. His curriculum vitae is attached.

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Dr. Philip Witorsch, Clinical Professor of Medicine and Adjunct Professor of Physiology, has been on the faculty of The George Washington University School of Medicine and Health Sciences since 1967. He is currently Director of the Program in Environmental Medicine and Toxicology in the Division of Pulmonary Diseases and Allergy of the Department of Medicine at The George Washington University Medical Center. He has acted as a professional consultant in the areas of pulmonary medicine and physiology, and environmental and occupational medicine and toxicology for a variety of clients and law firms and for federal, state, and local governmental agencies, including the

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Department of State, Department of Justice, Department of Labor, Occupational Safety and Health Administration, and Corporation Counsel of the District of Columbia. He is author or co-author of several review articles on the effects of environmental tobacco smoke on the respiratory system of adults and children, as well as co-author of a paper on the pharmacokinetics of nicotine and cotinine. His curriculum vitae is attached.

We have been asked by the Tobacco Institute to analyze the available data regarding the possible effects of environmental tobacco smoke (ETS) on the respiratory health and pulmonary function of children. We have also been asked to review the EPA's weight-of-the-evidence risk analysis on these subjects as presented in the draft document entitled Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children (U.S. EPA, 1990). We will initially address the relevant scientific literature and will conclude with a critique of the EPA risk analysis as it applies to this area.

The views expressed in this commentary represent our personal opinions and do not necessarily reflect those of our respective universities or any other institutions or entities with which we are affiliated.

I. SUMMARY

Based on our review of the relevant epidemiologic literature, the following points can be made regarding the reported associations between parental smoking and specific respiratory health end points addressed in the EPA draft document:

* The pertinent literature suggests an association between parental (primarily maternal) smoking and respiratory symptoms (e.g., wheeze, cough, phlegm production) and certain diseases (e.g., bronchitis, pneumonia, respiratory infections) in pre-school age children (43 studies).

* On the other hand, there is no consistent association between parental smoking and respiratory symptoms and disease in older children when specific clinical end points are considered (44 studies).

* There is also no consistent association between parental smoking and either impairment of pulmonary function in normal or asthmatic children (38 studies) or occurrence of middle ear effusion (17 studies).

The apparent consistency of the reported association between parental smoking and symptoms/disease in pre-school children could be due to one or more of the following factors:

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* Inadequate consideration of socioeconomic status and related variables.

* Greater sensitivity or increased exposure of younger children to ETS or other factors.

* Reported effects of maternal smoking on lactation or on the child's development in utero.

The inconsistent associations between ETS and symptoms/disease or decrements in pulmonary function in older children could be due to one or more of the following factors:

* Unreliability of the clinical data, particularly inaccuracies due to lack of verification.

* Age-dependent loss of sensitivity and/or exposure to ETS or other factors.

* Variability in the treatment of active smoking by children.

* Variability in adjustment for potential confounders (e.g., socioeconomic status, occupational exposures, history of respiratory illness, use of gas stoves).

* Overinterpretation of the data.

The EPA draft document concludes that parental smoking is associated with an increased incidence of most respiratory symptoms and diseases and with impaired pulmonary function. When reviewing these findings, the following characteristics of the EPA draft should be considered:

* Its incompleteness: Important scientific references have been omitted.

* Its superficiality: Data and concepts have been oversimplified, and the studies considered do not appear to have been reviewed critically.

* Its inaccuracy in reporting or interpreting the relevant literature.

* Its lack of objectivity, exemplified by selective dismissal of standards of statistical testing and deemphasis of critical confounding variables.

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II. INTRODUCTION

After reviewing the relevant literature, the National Research Council of the National Academy of Sciences (NRC, 1986)

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and the U.S. Surgeon General (1986) concluded the following with regard to the possible relationship between parental smoking and respiratory effects in children:

1. Parental smoking increases the risk of respiratory symptoms and illness in children, especially younger children.

2. Parental smoking may be associated with small decreases in pulmonary function in children and may impair pulmonary growth and development.

The EPA draft risk assessment contains a review of the literature that includes studies appearing after publication of the NRC and Surgeon General's reports. The general conclusion of the EPA draft with regard to pediatric implications is that ETS exposure adversely affects respiratory health and pulmonary function in children.

The purpose of the current presentation was to conduct an independent survey and objective analysis of the relevant literature to determine whether there is consistency among studies with regard to associations between ETS exposure and the respiratory health of children. Following this assessment of the available literature, we will attempt to provide explanations or mechanisms for observed consistencies and/or inconsistencies in the literature. The last section of this report will provide a detailed discussion and evaluation of the draft EPA document as it relates to this area.

III. SURVEY OF THE RELEVANT LITERATURE AND CRITICAL ANALYSIS OF THE DATA ON EFFECTS IN CHILDREN

Methodology used in the epidemiologic studies

1. Experimental design

Most of the epidemiologic studies under consideration were cross-sectional prospective or retrospective in design (comparing exposure groups at a particular point in time), and a few were case-control studies (where the incidences of parental or household smoking were compared). A few studies were longitudinal in design or had a longitudinal component. These, where the subjects were examined over the course of years, were designed to detect age-dependent phenomena or, in the case of pulmonary function, effects on lung growth and development.

2. Questionnaires

Only epidemiologic studies have investigated the relationship between ETS exposure and respiratory effects in offspring, and with the exception of investigations by Strachan

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et al. (1989, 1990), they have used the surrogate of parental or household smoking as their only index of children's ETS exposure (Rubin and Damus, 1988). Information on smoking by other family members and by the children under study, family health history, and other relevant data were most often obtained solely by use of questionnaires, although in some cases additional information was obtained by physical examination or from health records (Witorsch, 1990). The questionnaires usually were derived from the ATS-DLD instrument, a derivative of the British Medical Research Council questionnaire (Witorsch and Witorsch, 1989; Witorsch, 1990). The questionnaires typically were completed by the parents, with or without supervision by the investigators, although in some cases older children were asked about their personal smoking habits.

3. Exposure classification

In the reviewed studies, children generally were classified according to their parents' smoking status. In most cases, the mother's smoking status was used to determine whether to classify the child as ETS exposed or unexposed. In several of the studies, an attempt was made to obtain a somewhat more quantitative measure of exposure, through determination of the amount of smoking by the parent or the number of smoking family members. Only in the work of Strachan et al. (1989, 1990), however, was any attempt made to verify objectively the child's relative ETS exposure by means such as biomarkers or air sampling (Rubin and Damus, 1988; Spitzer et al., 1990; Witorsch, 1990).

4. Health-related and physiological end points examined

In a number of studies involving younger children (under school age), the subjects were categorized according to incidence of respiratory symptoms or disease. These included broad categorizations (such as "respiratory infections," "respiratory illness," or "chest illness"), more specific entities (such as cough, phlegm, or wheeze), and illnesses (such as chest colds, pneumonia, tracheitis, bronchitis, bronchiolitis, asthmatic bronchitis, and asthma) (Witorsch, 1990).

Although a number of investigations of school-age children also assessed respiratory symptoms and/or disease, several additional studies evaluated possible effects of ETS exposure on pulmonary function, as determined by differences in spirometric end points. The end points examined in most studies are derived from the forced vital capacity (FVC) maneuver, the amount of air (L) that can be expelled from the lungs by a maximal forced expiratory effort subsequent to a maximal forced inspiratory effort. The two most common derivatives of the FVC used in the studies in question were FEV_1 and FEF_{25-75}. The FEV_1 is the volume of air (L) that is expelled during the initial second of the FVC. In some studies in children, $FEV_{0.75}$ (volume of air expelled during the first 0.75 second of the FVC) was used as an alternative to FEV_1. It has been reported that in a significant

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proportion of children, the FEV_1 is almost as large (99%) as the FVC, and consequently it has been suggested that $FEV_{0.75}$ is a preferable alternative to FEV_1 for children (Chan and Silverman, 1989). The FEF_{25-75} is a measurement of the rate of airflow (L/sec) between 25% and 75% (or midportion) of the FVC maneuver. Additional end points compared in some studies included $Vmax_{50}$ and $Vmax_{75}$ (maximal flow rates [L/sec] at 50% and 75% of the TLC [total lung capacity], respectively) and PEFR (maximal flow rate [L/sec] attained during the FVC maneuver or measured directly, using a device such as a peak flow meter).

Spirometric performance is dependent upon age, height, and sex. Therefore, determining whether an individual exhibits normal or abnormal function requires comparison of measured values with predicted values based upon age, height, and gender (Bates, 1989). Performance on spirometric tests also may be affected by a technician's competence, the specific type of spirometer used, and the attitude of the subject undergoing the test (Bates, 1989).

The FEV_1 is generally regarded as a reproducible, although relatively insensitive, method to detect certain types of pulmonary dysfunction and disease (Bates, 1989). It has been suggested that FEF_{25-75} is particularly sensitive to and reflective of abnormalities in bronchioles less than 2-3 mm in diameter, but this suggestion remains controversial (Burrows et al., 1983; Miller, 1986). FEF_{25-75}, as well as other analogous parameters, are considered to be much more variable than FEV_1 within and between individual subjects. For example, the normal ranges of variation within a population for FVC, FEV_1, and FEF_{25-75} are, respectively, about 20%, 20%, and 40%, and decrements exceeding this magnitude below predicted values are regarded as being abnormal for these respective parameters (Bates et al., 1989; Lebowitz et al., 1987). The within-subject variation for FVC, FEV_1, and FEF_{25-75} is estimated to vary by as much as 1/4 and 1/2 of the population variation on a daily and weekly basis, respectively (Lebowitz et al., 1987). Variation in pulmonary function for children is estimated to be comparable to that of adults and has been regarded as a source of concern in epidemiologic studies (Strachan, 1989).

Pulmonary problems can exist, of course, without causing deviations from the normal in pulmonary function tests. If tests show consistent deviations, this raises the possibility that there is an underlying problem, but the existence of a minor problem may not always be associated with abnormal pulmonary function test results. For example, Slonim and Hamilton (1981) state that "pulmonary function tests cannot detect slight loss of functioning pulmonary tissue or the presence of small regions in the lungs that have neither ventilation nor perfusion . . . [T]ests do not reveal dysfunction in all types of bronchopulmonary disease." On the other hand, isolated deviations, especially in such parameters as FEF_{25-75}, may not necessarily reflect clinically or physiologically significant

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dysfunction. These limitations notwithstanding, spirometric tests are often useful in detecting and identifying the type of dysfunction that has been associated with active smoking.

Review of published studies

1. Studies of respiratory effects in pre-school-age children

A compilation of the 44 epidemiologic studies dealing entirely or predominantly with pre-school-age children is presented in Table I (see tables in Section V following the References Section). These studies dealt entirely with respiratory symptoms and disease.

With some exceptions, the relevant studies have reported an association between parental, usually maternal, smoking and an increased incidence of respiratory symptoms (such as wheezing, cough, and phlegm production) and/or illness (such as bronchitis, tracheitis, pneumonia, chest colds, bronchiolitis, and respiratory infections) in infants and pre-school children (0-5 years of age). The odds ratios were usually 2.0 or less. Several of the studies have reported a dose-response relationship, where the frequency of respiratory problems in the children was proportional to the number of cigarettes reported to have been smoked by the parents and/or the number of parental (or total household) smokers.

Among the studies listed in Table I, a few addressed the issue of possible age-dependency of effects (i.e., Colley et al., 1974; Rantakallio, 1978; Fergusson et al., 1981; Fergusson and Horwood, 1985; Chen et al., 1988). The authors concluded that, for preschool children, the apparent association between parental smoking and respiratory symptoms or disease was greatest in the youngest children (under two years of age) and declined as the children aged.

2. Studies of respiratory effects in school-age children

a. Respiratory symptoms and disease

A compilation of the 44 epidemiologic studies dealing entirely or predominantly with school-age children is presented in Table II. Although the majority of the published studies reported one or more significant relationships between parental (usually maternal) smoking and various respiratory symptoms or diseases, the specificity of these apparent associations varied considerably. Examination of the summary values for positive versus negative findings suggests that there is considerable inconsistency with regard to ETS and respiratory symptoms and disease in older children. When an association was evident, there was considerable variation from one study to the next with

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regard to the particular symptom(s) or illness(es) considered. As shown at the bottom of table II, a particular clinical end point is usually confirmed no more than half of the time.

b. Middle ear effusion

The seventeen published studies addressing whether middle ear effusion (as a sign of chronic middle ear disease) is related to ETS exposure are listed in Table III below. These studies were conducted in both pre-school and school-age children.

Again, the data are not consistent. Less than half of the published studies reported statistically significant associations between middle ear disease and ETS exposure, while the majority found no such association. Furthermore, no apparent age-dependent relationship is evident.

c. Pulmonary function

Some 38 epidemiologic reports have been published addressing the issue of whether there is a relationship between parental smoking and pulmonary function in children. These are listed in Table IV, along with their geographical locations, the numbers of subjects included, and the subjects' inclusive ages. A number of these published papers are reports of two or more investigations of the same study population and are thus not entirely independent assessments. These include studies of East Boston, six U.S. cities (in the states of KS, OH, MA, MO, TN, and WI), Tucson, AZ, and Vancouver, BC, Canada.

Table V summarizes the findings of the epidemiologic studies of parental smoking and pulmonary function in nonasthmatic children. These data indicate that changes in most of the parameters evaluated were not consistently associated with parental smoking, an observation also noted by Guyatt and Newhouse (1985). Furthermore, the presence or absence of an association for pulmonary function parameters was not dependent on the size of the cohort. Although 11 of 15 studies reported a decrement in FEF_{25-75} in nonasthmatic children of smokers, primarily smoking mothers, there are a number of considerations that affect the interpretation of the data. In one study (Tager et al., 1979), the overall decrement was not statistically significant; statistical significance was demonstrated only for trend (among children with 0, 1, or 2 smoking parents), and only when smoking children and their siblings were included. Furthermore, in three of the studies, the decrement in FEF_{25-75} was observed in females (Tashkin et al., 1984; Vedal et al., 1984; Chen and Li, 1986) and not males, while in another, the decrement in this parameter was reported in males (Masi et al., 1988) but not in females. The reported percentage changes in this parameter, when values were reported, were typically small (in the 2-6 per cent range), and were within the normal ranges

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for such parameters (Bates, 1989), with the exception of values from two studies (O'Connor et al., 1987; Yarnell and St. Leger, 1979).

Five longitudinal studies have attempted to relate parental smoking to changes in lung growth in children. While two have reported an association (Tager et al., 1983, 1985; Berkey et al., 1986), the three others failed to do so (Dodge, 1982; Lebowitz et al., 1987; Dijkstra et al., 1988). Both Tager (Tager et al., 1987) and Lebowitz (Lebowitz and Holberg, 1988) have attempted to reconcile the differences in the findings of their longitudinal investigations, which were not seen as being due to differences in their statistical analyses. Among the possible reasons for differences in the two outcomes are confounding variables (e.g., differing climates in the two study areas). This illustrates the complexity of considering such variables.

When the data on asthmatic children only are examined (Table VI), no obvious conclusions can be drawn, as the number of available studies is small and the data are inconsistent. However, the series of studies conducted by Murray and Morrison in Vancouver, B.C., suggest that many factors influence the relationship between parental smoking and pulmonary function in asthmatic children (Table VI). Although their initial study revealed that maternal smoking was associated with decrements in FEV_1 and FEF_{25-75} (Murray and Morrison, 1986), a subsequent study on an enlarged cohort of children revealed that maternal smoking effects were seasonal, demonstrable during the cold-wet season (Oct.-May) but not during the warm-dry season (June-Sept) (Murray and Morrison, 1988). In their most recent study (Murray and Morrison, 1989), they explored the impact of gender and age on smoking effects. In boys, maternal as well as paternal smoking was associated with decrements in FEV_1 and FEF_{25-75}, while in girls maternal smoking apparently had no effect on pulmonary function parameters. When examined on the basis of age in children of both sexes, maternal smoking had no effect on pulmonary function in children aged 1-11 years while an effect on these parameters were seen in children aged 12-17 years.

In several studies involving nonasthmatic children, FEV_1 (or $FEV_{0.75}$) and FEF_{25-75} were measured concurrently. In another attempt to assess the consistency of the pulmonary data, results of these studies were compared, and these comparisons are shown in Table VII. Decreases in both parameters were observed in seven of the sixteen studies, while two reported a decrease in FEV_1 without a decrease in FEF_{25-75}, five studies reported the converse situation, and in two, no effect was observed in either parameter.

Regarding asthmatic children, Murray and Morrison (1986, 1988, 1989) as well as other workers have reported that FEV_1 and FEF_{25-75} were both affected or both remained unaffected in all cases when examined concurrently (Table VI).

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When the results from successive reports on the same cohort are examined (Table VIII), one can see that the data from East Boston and "Six U.S. Cities" are somewhat inconsistent, while those from the Tucson study are largely consistent in showing no effect over time.

One consistency noted previously is the reported dose-response relationship between parental smoking and pulmonary performance (Witorsch and Witorsch, 1989). In a number of studies where an effect was observed for FEV_1 (or $FEV_{0.75}$) and FEF_{25-75}, the magnitude of both parameters varied inversely with the amount of tobacco consumed by the parent or the number of household smokers (cf., Table 3 in Witorsch and Witorsch, 1989).

d. Bronchial responsiveness

The effects of parental smoking on bronchial responsiveness in normal and asthmatic subjects have been examined using bronchoconstrictors or bronchodilators. Weiss et al. (1985) and O'Connor et al. (1987), using cold air, and Corbo et al. (1989), using methacholine, failed to show any significant effect of parental smoking on bronchial responsiveness in nonasthmatic children. Soto et al. (1985) were unable to show a relationship between family smoking history and infant responsiveness to the bronchodilator, salbutamol, in children with respiratory syncytial virus bronchiolitis (although they reported a 14% reduction in specific conductance [i.e., airway patency] associated with maternal smoking in this group). Alternatively, Ekwo et al. (1984) reported increased responsiveness to isoproterenol among children of smoking parents, while Martinez et al. (1988) observed an increased bronchial responsiveness to carbachol in boys but not in girls. Recently, Strachan et al. (1990) reported finding no association between salivary cotinine in children (as a marker for ETS exposure) and exercise-induced bronchospasm (decreased FEV_1).

O'Connor et al. (1987) reported hyperresponsiveness to cold air challenge associated with maternal smoking in asthmatic children, but the effect was not statistically significant. Martinez et al. (1989) noted that the responsiveness to carbachol they found in normal children of smoking parents was enhanced in asthmatic children. Murray and Morrison (1986) also reported a four-fold increase in bronchial responsiveness to histamine associated with maternal smoking in asthmatic children. They also noted that the same factors that affected baseline pulmonary function in asthmatics, namely climate, gender, and age, also influenced the association of maternal smoking with increased bronchial responsiveness. For example, they reported that the maternal smoking effect on bronchial responsiveness of asthmatic children to histamine was statistically significant during the dry-warm season. Further, they reported that a statistically significant effect of maternal smoking on bronchial responsiveness to histamine was found in male but not in female asthmatic children (Murray and Morrison, 1989). The effect of

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maternal smoking on bronchial responsiveness to histamine in asthmatic children appeared to be age-dependent. While a statistically significant association was observed between the ages of 12 and 17 years, no such effect was seen in children aged 7-11 years (Murray and Morrison, 1989).

It is interesting to note that a recent report of a longitudinal study involving the East Boston cohort could find no apparent relation of maternal or paternal smoking to the development of asthma in children, as reflected in the age of first onset of asthma (Sherman et al., 1990).

Analysis: The basis for associations and lack of associations in studies relating ETS exposure to respiratory effects in children

Our survey of the literature reveals the following:

* The studies report an association between parental smoking and respiratory symptoms and certain diseases in young (pre-school) children.

* The data pertaining to parental smoking and respiratory symptoms and disease in school-age and older children lack consistency.

* The data pertaining to parental smoking and pulmonary function effects in children, including effects on lung development and growth, lack consistency.

1. Explanations for the apparent age-dependency of reported effects associated with parental smoking in pre-school children

a. ETS exposure

As noted above and previously discussed in the literature (Guyatt and Newhouse, 1985; NRC, 1986; Surgeon General, 1986; Witorsch, 1990), investigators who have addressed the question have found an apparent age-dependency of the association of respiratory symptoms/disease with parental smoking. Since this observation has been reported in only a small number of studies, it will require further confirmation. However, if the association persists, it may be due to a number of possible causes. One possibility is that there is an actual cause-and-effect relationship, as ETS exposure may be greatest during the first year or two of life. At this time, the mother-child relationship is the most intimate (Fergusson et al., 1981; Fergusson and Horwood, 1985), and ETS exposure may be more intense than it is later. Additionally, it is possible that the young child, with its immature lungs, could be more sensitive to a number of environmental factors, such as ETS.

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An age-dependent association, however, is also consistent with a non-ETS-related explanation for the observed relationship between parental smoking and children's respiratory disease; living in the home of a smoker may tend to put a child at risk for other reasons, such as exposure to more parental respiratory infections (NRC, 1986). The currently available data do not, however, distinguish between these explanations and alternatives.

Several factors other than ETS (i.e., airborne constituents of tobacco smoke), either biological or non-biological, alone or in combination with one another, may account for the reported association between parental smoking and impaired respiratory health in younger children. Among the possible biologic mechanisms other than ETS exposure are pre- or perinatal effects (e.g., effects of maternal active smoking during pregnancy or lactation). Among the predominant nonbiological factors are socioeconomic status (SES) and related variables.

b. Effects of maternal smoking on in utero development and/or lactation

Smoking by the mother during pregnancy might transplacentally deliver substances to the fetus that could affect the offspring's ability to ward off disease postnatally. An association between maternal active smoking during pregnancy and adverse effects, such as low birth weight, on growth and development of offspring has been reported (Abel, 1980).

Recent data suggest that low birth weight (under 2000 g) is a potential confounder of maternal smoking effects on the respiratory system of children. Chan et al. (1989b) reported that while maternal smoking was not associated with increased incidence of wheeze in 7-year-old children of normal weight at birth, maternal smoking was associated with an increased incidence of wheeze in children of that age who were of low birth weight. In addition, other recent studies report that maternal smoking during pregnancy increases the risk of infant mortality (Kleinman et al., 1988), particularly that due to respiratory disease (Molloy et al., 1988). Furthermore, maternal smoking has been reported to be associated with early weaning and impaired suckling-induced prolactin release (Andersen et al., 1982), and tobacco constituents are found in breast milk of smoking mothers (Woodward et al., 1986; Schwartz-Bickenbach et al., 1987). An effect of maternal smoking on the quality of breast milk could affect its immunologic potency, and hence the offspring's ability to resist disease. It is also provocative to note that the apparent inverse relationship between smoking and duration of lactation has relevance in view of recent reports suggesting that artificial feeding (as opposed to breast feeding) is a risk factor in respiratory illness (McConnochie and Roghmann, 1986; Geller-Bernstein et al., 1987; Chen, 1989).

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Taylor and Wadsworth (1987) determined that reported rates of admissions to hospitals for diseases of the lower respiratory tract were as great for children whose mothers stopped smoking during pregnancy as for those whose mothers smoked both during and after pregnancy. Admission rates for children whose mothers started smoking only after pregnancy were no higher than those for children whose mothers were non-smokers. Although postnatal maternal smoking appeared to be related to the incidence of bronchitis in children, the relationship was not as strong as that between the offspring's bronchitis and maternal smoking during pregnancy. Additionally, Van Cauwenberge and Kluyskens (1984) noted that an increased incidence of otitis media in children was associated with maternal smoking during gestation. Such results raise the possibility that maternal smoking during pregnancy could be the source of subsequent respiratory health effects that have been assumed by some to be attributable to postnatal exposure of the child to ETS.

On the other hand, in utero and/or lactational mechanisms cannot explain an apparent association between paternal smoking and respiratory health effects in young children reported from Shanghai households (Chen et al. 1986, 1988; Chen, 1989). Here, none of the mothers were reported to be smokers. Thus, it is apparent that the relationship between parental smoking and possible respiratory effects in offspring is complex and not yet adequately understood.

c. Socioeconomic status

That socioeconomic status may affect children's respiratory health is indicated by the data of Kerigan and coworkers (1986) on a cohort from Hamilton, Ontario. They found that parental smoking was negatively related to family income, and that smoking was positively correlated with a number of SES-related variables that have been associated with poor respiratory health. These variables included diminished outdoor air quality, increased parental coughing, greater use of gas stoves, frequent address changes, and more crowded housing. The findings of Harlap and Davies (1974) further suggest how SES-related factors may confound effects presumed to be caused by children's exposure to parental smoking. According to those workers, parental smoking was associated with an increased incidence of hospitalizations of infants because of injury and poisoning. Such an outcome is suggestive of parental neglect (Surgeon General, 1979), which could also lead to a greater incidence of respiratory illness. Further, according to Harlap and Davies (1974), the smoking mothers in their study population located in West Jerusalem, Israel, were actually more likely to be of a higher SES (the converse of the typical situation in North America). If some characteristics that made such mothers smokers also are relevant to the manner in which they rear their young children, such factors might have an even greater effect in low SES smoking mothers who are more typical in the U.S. The findings of Ogston et al. (1987) that alimentary illnesses (diarrhea, vomiting, and

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colic) were apparently associated with parental smoking lend credence to the assumption the such associations can be noncausal and may be due to such factors as parental neglect.

Socioeconomic status is a complex of a number of factors, and it is not simple to adjust for in epidemiologic research (Witorsch, 1990). Among the elements of SES, the most important may be education (especially maternal education), income, occupation, and ethnicity. A weighted formula involving these components has been proposed to correct for SES in health-effects studies (Green, 1970). Nevertheless, the above factors often have been addressed either incompletely or not at all in the studies of ETS and infant respiratory health. Finally, even with the use of the most rigorously weighted estimates of SES, it may be extremely difficult to predict the potential effect of such factors as family attitudes and practices concerning prenatal care, early postnatal care, stress management, nutrition, and exercise on the outcome of epidemiologic studies.

Other factors that are related to SES may also have particular bearing on the relationship between parental smoking and respiratory health in young children. Deserving of further comment among these are attendance at day care centers and the presence of older siblings.

d. Day care centers

In the literature on parental smoking and respiratory health of children, almost no attention has been paid to a major factor increasingly impinging on the health of younger children--enrollment in day care facilities. A number of studies have established that young children who attend day care facilities are more likely to suffer from respiratory illnesses than are children who are cared for by family members at home (e.g., Strangert, 1976; Stahlberg, 1980; Haskins and Kotch, 1986; Fleming et al., 1987; Harsten et al., 1990); the same is said to be true of otitis media (e.g., Fleming et al., 1987; Harsten et al., 1990). Children in day care have even been found to have considerably higher incidences of antibiotic-resistant strains of Streptococcus pneumoniae than other children (Henderson et al., 1988). The total burden of respiratory illness is apparently not increased by exposure to day care, but the illnesses tend to occur at younger ages (Aronson and Osterholm, 1986). Since smoking tends to be correlated with lower socioeconomic status (Rush and Callahan, 1989), smokers' children may be overrepresented among those attending day care centers, thus giving the appearance of a causal relationship between maternal smoking and respiratory illness in preschool children, especially the youngest children.

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e. Presence of older siblings

Family size is another potential confounding factor that has received little attention in most studies of parental smoking and children's respiratory health. In 1970, Colley reported that children from large families had a greater incidence of respiratory symptoms than children from small families. More recently, McConnochie and Roghmann (1986b) found that the presence of older siblings was associated with bronchiolitis in both normal and asthmatic children, and the older and more numerous the siblings, the stronger the relationship. This finding was attributed to greater likelihood of exposure to respiratory viruses introduced by the older siblings, as had been shown previously by Brimblecombe et al. (1958) and by Hall et al. (1976).

Two other potential confounding factors that may be a reflection of SES also are worth noting, i.e., the use of gas stoves in the home and history of family illness. Since they have a bearing on both younger and older children, these factors will be discussed below.

2. Explanations for lack of consistency of association in older children

a. Disappearance of reported association of ETS and health effects as children age

The diminished consistency of the association between parental smoking and respiratory health in older children may indicate that as the child ages, his or her possible sensitivity to ETS or to pre- or perinatal effects of maternal smoking diminishes (i.e., this reflects an age-dependent phenomenon) or that intimacy with the mother decreases.

b. General problems associated with epidemiologic studies

General problems associated with epidemiologic methodology that can contribute to lack of consistency have been noted by others. For example, Spitzer et al. (1990) state that "Some of the larger cohort studies did not examine the effect of passive smoking in order to explore a specific hypothesis set forth in advance. This means that some of the data were overexamined, or used to derive post hoc conclusions." They state further that "The design of some studies was marred by failure to define outcomes and validate questionnaires in a manner consonant with normative practice." Guyatt and Newhouse (1985) have noted that in many cases in which data were obtained by interviewers, it was not clear whether the interviewers were aware of the study's hypotheses. Such an awareness could introduce bias into the reporting of end points or exposure. Further, it is well recognized that--relative to active smoking--the reported effects

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of ETS exposure are much smaller, ETS exposures are more variable, and the ETS-exposed population is less well defined (Spitzer et al., 1990).

c. Uncertain reliability and validity of clinical data

Complications arise when questionnaires are used as the source of health-related data. Without validation from clinical data, parents' memories and characterization of respiratory events involving their children may be inaccurate. Such information could be influenced by such factors as parents' education, access to and quality of professional medical care, and duration of time between the reported symptom and completion of the questionnaire. For example, it is conceivable that the considerable variability within specific respiratory problems in older children (Table II) could reflect the difficulty a parent (lacking medical expertise) has in differentiating between such entities as "asthma," "wheeze," "cough," and "bronchitis."

As alluded to above, several studies have noted an association between the reported incidence of respiratory problems in parents and those of their children, suggesting the existence of either parental recall bias or the transmission of infection from parent to child (Colley et al., 1974; Ware et al., 1984; Surgeon General, 1979). Inaccuracies inherent in maternal recall recently have been noted by Vobecky et al. (1988). Furthermore, the usefulness of the ATS-DLD questionnaire in studies of asthma has been questioned by Enarson et al. (1987). Actual medical records and clinical observation are no doubt more accurate and reliable than unverified parental responses. However, such information also may be incomplete, anecdotal, or not acquired in an unbiased, scientific fashion.

The finding of Colley (1974) that smoking parents had a higher incidence of respiratory infections than did nonsmoking parents and that the parents' incidence of respiratory infections was correlated with that of their children suggests that cross infection may have played a role in the findings in children. The potential impact of parental illness on childhood illness, often inadequately addressed in epidemiologic studies, can be further appreciated from consideration of the data of Koo et al. (1988), who compared the prevalence of respiratory illnesses in primary school age children (grades 2-6) of nonsmoking mothers in Japan and Hong Kong. Although some 60 per cent of the Japanese fathers smoked, versus less than 36 per cent of Hong Kong fathers, the prevalence of respiratory illnesses was much greater among the children in Hong Kong. This was true of cough and/or phlegm, wheeze, pneumonia, chest illnesses per child, and multiple illnesses per child, but there were no differences in the incidence of allergic rhinitis or asthma. Interestingly, the frequency of respiratory symptoms/illness in the children of both populations was significantly correlated with the frequency of such conditions in their mothers, suggesting that parental (or at least maternal) illness is a risk factor for children apart from

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any correlation with maternal smoking, as reportedly none of these mothers smoked. This possibility is supported by the findings of Koo et al. (1988) in children of nonsmoking women that maternal respiratory illness was positively correlated with such conditions in their offspring.

3. Exposure assessment and misclassification bias

a. Inadequacy of the questionnaire as the basis for ETS exposure classification

Rubin and Damus (1988) point out that the various studies pertaining to ETS exposure in children have often varied in their definition and quantification of smoke exposure obtainable from questionnaire data. Numerous sources of error, including erroneous reporting of parental smoking status (NRC/NAS, 1986; Lee, 1988) and change of parental smoking status (Berkey et al., 1986), have been recognized with regard to using parental smoking as the index of ETS exposure in children.

While early reports of a correlation between body fluid levels of cotinine (a metabolite of nicotine) in children and the number of smokers in the family suggested that questionnaire data might be useful as an indicator of ETS exposure (Greenburg et al., 1984; Jarvis et al., 1985), recent data do not support that conclusion. Strachan et al. (1990) reported that the 10 per cent of the children in their cohort with the highest salivary cotinine concentrations (upper two quintiles) came from households classified as nonsmoking and that three-fourths of the children from "nonsmoking" households had detectable salivary cotinine concentrations. Ronchetti et al. (1990) reported that detectable levels of salivary cotinine were found in 13 per cent of the children living in families claiming to be nonsmoking, while detectable salivary cotinine was found in only 60 per cent of children from putative smoking families.

Furthermore, the available data from the one study in school-age children that examined an association between salivary cotinine levels (as a marker for ETS exposure) and effects on the respiratory system are not compelling. Strachan et al. (1990) reported that for most symptoms (runny nose, cough, wheeze, sore throat, ear trouble, hay fever) no association was observed. A statistically significant association was reported only for "chesty colds" in the past year. Most of the baseline pulmonary parameters (FVC, $FEV_{0.5}$, FEV_1, FEF_{25-75}, PEF, FEF_{25}, FEF_{50}, FEV_1/FVC, FEF_{25-75}/FVC, and FEF_{75-85}/FVC) as well as exercise-induced bronchospasm (decreased FEV_1) were not associated with salivary cotinine levels. The only significant associations reported were for FEF_{75-85} and FEF_{75}, and the reported decrements were small. The statistical methodology used could have resulted in false estimates of significance, as the statistical analysis did not adjust for multiple comparisons. In addition, the

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clinical and physiological relevance and significance of terminal flow rates, such as FEF_{75-85} and FEF_{75}, is highly questionable (Miller, 1986; Bates, 1989).

While the questionnaire appears to be somewhat unreliable for estimating ETS exposure, similar reservations may also apply to the use of body fluid cotinine for this purpose. Recent information regarding the fate of airborne nicotine and problems associated with nicotine pharmacokinetics in individuals indicate that body fluid cotinine provides, at best, only a semiquantitative estimate of ETS exposure (Balter et al., 1988; Lee, 1988).

b. Bias due to active smoking by the child

According to certain studies, active smoking by the child could be a source of bias in studies of children's respiratory illness or pulmonary function, in that active smoking by the child is considered to be a much more important factor than is ETS exposure (Guyatt and Newhouse, 1985). Also, smoking parents are more likely to have smoking children, a situation analogous to marital concordance, and a considerable percentage of children are smokers (Tager et al., 1976; NRC, 1986; Surgeon General, 1986; Lebowitz et al., 1987; O'Connor et al., 1987; Charlton and Blair, 1989). For example, Charlton and Blair (1989) reported that 37% of their sample of 12 and 13 year old children admitted to having smoked at some time or to being current smokers. They considered this figure to be a low estimate, in that children who were absent on the day the questionnaires were completed were more likely to have been smokers than were those who were present. These authors also stated that children of smokers were twice as likely to be smokers themselves, in comparison with children of nonsmokers. According to Kerigan et al. (1986), 24% of the children between the ages of 9 and 13 years in their study cohort had smoked previously. As the children grew older, a greater proportion of them smoked, so that by the age of 13 years, 50% admitted to having smoked, with 32% smoking in the previous four weeks.

In a number of the studies involving older children, there was either inadequate consideration of or lack of appropriate control for active smoking by the children (Witorsch, 1990). In some studies, there was no apparent consideration of the possibility of smoking by the subjects; in others, parents were asked to provide information on their children's smoking, although a parental source for such information is likely to be inaccurate. Even in studies where children were questioned in the absence of their parents regarding their personal smoking habits, it was often assumed that children below a certain age did not smoke (e.g., Burchfeil et al., 1986). Depending on the specific study, this cutoff age varied from 9-15 years, and while some studies excluded smoking children, others did not (Witorsch and Witorsch, 1989).

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The reported figures in the literature for childhood smoking may be on the low side, as they are generally derived from questionnaires, and children are likely to underreport a disapproved behavior (Guyatt and Newhouse, 1985). This concept has also been suggested by the findings of Kerigan et al. (1986), as they acknowledge that their estimates were not validated by direct measures, and the percentage of children admitting to having smoked in the previous four weeks did not increase with age, contrary to what would be expected if they were being entirely candid. Since active smokers have been reported to be more likely to have increased respiratory symptoms or disease and decreased pulmonary function (Tager et al., 1979; Lebowitz et al., 1987), the inclusion of a significantly greater proportion of actively smoking children in the groups with smoking parents could result in an apparent effect of ETS exposure, even in the absence of a true effect. The concept that active smoking might explain some of the apparent ETS data was proposed by Tashkin and coworkers (1984) with reference to their finding that ETS-exposed older girls (12-17 yr old) in their study exhibited decrements in small airway function, while younger girls (7-11 yr old) did not.

4. Other potential confounders

Among the other factors contributing to the variability in the association between parental smoking and respiratory health in older children are the variables discussed above in relation to socioeconomic status. Pulmonary function in children, in particular, can be influenced by motivation, learning, and SES and is subject to chance variation (Witorsch and Witorsch, 1989). Other sources of variability of outcome in older children are occupational exposures (which may be more likely in older children), gas stove usage, history of respiratory illness, and heredity. Several of these deserve further comment.

a. Presence of gas stoves in the home and other environmental factors

According to the results of Speizer and coworkers (1980), children living in homes with gas stoves had a greater incidence of respiratory disease and lower levels of FEV and FVC (corrected for body height) than did those from homes with electric stoves. These findings held true even following adjustment of the data for parental smoking and social class. Possible explanations for this finding include the presence of high peak indoor levels of NO_2 that were observed to occur regularly in the kitchens of homes with gas stoves. Recently, Berwick et al. (1989) reported a statistically significant association between ambient NO_2 concentrations (from unvented combustible sources, such as kerosene heaters) and lower respiratory symptoms (such as cough, wheeze, bronchitis, and asthma) in children under seven years of age. This association was not apparent in children aged seven years or older. Previous respiratory illness and higher socioeconomic status were also significantly and independently associated with reported illness, but exposure to household

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smoking was not associated with respiratory symptoms in either age group. Interestingly, others have found not only that the presence of gas cooking stoves was correlated with increased serious respiratory illness but also that smoking parents were more likely to have gas stoves in their homes (Ekwo et al., 1983). Other factors, such as the use of coal-fired heaters or stoves and the presence of mold and dampness in the home, have been reported to be associated with respiratory problems, including wheeze, cough, and absence from school (Strachan and Elton, 1986). As discussed previously, Murray and Morrison (1988) have reported that the association between maternal smoking and pulmonary function in asthmatic children is dependent upon the climate being wet and damp. If such factors are also unevenly distributed among homes of smokers and nonsmokers, this confounding would, unless corrected for, tend to increase further the apparent effect of parental smoking. Comparable findings prompted Spitzer et al. (1990) to call for further research on the interactions between indoor air contaminants, including indoor dampness, molds, and nitrogen dioxide, as well as tobacco smoke, and indeed, Ross et al. (1990) recently published a study linking wheezing in children with the presence of gas heating and cooler, damper bedrooms.

b. History of respiratory illness

Children who have had bronchitis or pneumonia early in life appear to be compromised with regard to pulmonary function in subsequent years. This finding by Leeder and coworkers (1976b) further confounds the issue of maternal smoking and pulmonary function of children, as it is not known whether the respiratory illness is an effect of maternal smoking during pregnancy or of parental smoking after the birth of the child, or if both increased incidence of respiratory illness and parental smoking are correlated with other factor(s) that are the actual cause of illness. The observed decrement in pulmonary function could be caused by some aspect of parental smoking, by lasting effects of the child's respiratory illnesses, by one or more other factors correlated with the above, or by some combination of these. Similarly, Stern et al. (1990) reported that children hospitalized in the first two years of life exhibited higher risks of respiratory symptoms and illness. They also had decrements in pulmonary function when examined at 7-12 years of age.

c. Heredity

According to a variety of studies in the literature, pulmonary function measurements appear to be aggregated by families (Higgins and Keller, 1975; Tager et al., 1976; Schilling et al., 1977), a finding further confirmed by data derived from studies of twins (Hankins et al., 1982; Hubert et al., 1982). These considerations led Lebowitz et al. (1984) to take into account both the children's body habitus and that of the father (which correlated more closely with that of the children than did

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the maternal body habitus). When this was done, it was found that the apparent relationship between parental smoking and impairment of children's lung function could no longer be observed. Unfortunately, this adjustment has not typically been made in studies of parental smoking and children's pulmonary function. Similarly, McConnochie and Roghmann (1986) reported that maternal smoking (or household smoking) was a risk factor for wheeze only in children (6-10 years of age) with a family history of allergy, suggesting that genetic predisposition may be required for manifestation of any ETS effect.

5. Other considerations

a. Apparent quantitative relationships

The apparent quantitative relationship between decrements in pulmonary function and the amount of parental smoking and/or the number of household smokers may have several explanations. Dose-dependent effects may be a reflection of the amount of ETS exposure, or they may be quantitatively related in an indirect fashion to aspects of misclassification error and/or SES. The incidence and intensity of active smoking in children or confounding variables usually associated with SES (such as outdoor air quality, gas stove usage, etc.), for example, may at times vary in proportion to the number of household smokers or the number of cigarettes smoked by the parent. The phenomenon of apparent dose-dependency as it relates to parental smoking and pulmonary function is provocative and should be examined further.

b. Over-interpretation of the data

In a number of the epidemiological studies, the authors ignore statistical criteria and emphasize trends that are not statistically significant as being meaningful. This tendency is biased and can perpetuate misunderstanding. While lack of statistical significance does not eliminate the possibility of a real association (since it could merely reflect high variability or an inadequate number of subjects), studies should be designed so as to obtain less equivocal findings rather than provide potentially misleading information. Lack of statistical significance should be considered as being consistent with the null hypothesis, unless proven otherwise.

Conclusions

Rubin and Damus (1988) recently evaluated 30 studies dealing with ETS exposure and children's health. These papers were quantitatively rated on the basis of several individual criteria (such as data collection, estimates of smoke exposure, definition of illness). They noted that although a few of the studies were well-designed, most had significant design flaws that prevented unqualified reliance on their conclusions.

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Our analysis employed a different approach. Rather than rating individual studies, we surveyed the data base for the following three categories in terms of consistency: 1) respiratory health effects in young children, 2) respiratory health effects in older children, 3) pulmonary function in older children.

Although the association between parental smoking and increased incidence of respiratory symptoms and diseases in young children is observed repeatedly, the mechanism for this association remains unexplained. Among the possibilities worth considering are ETS, pregnancy and/or lactation-related effects, and SES-related confounders. The lack of consistency of this association as the child ages, also noted in relation to pulmonary function, is also unexplained. Among the possible explanations for this apparent age-dependent decline are changes in the susceptibility to or intensity of ETS exposure, inaccuracies in the data obtained from questionnaires (e.g., unvalidated clinical data and smoking status misclassification), and confounding variables. We agree with Coghlin et al. (1989), who state that the use of validated questionnaires and diaries, combined with personal monitoring, is needed in order to "reduce misclassification in future epidemiologic studies and allow . . . more accurate investigations of the relation between environmental tobacco smoke and adverse health effects."

IV. DISCUSSION OF THE DRAFT EPA DOCUMENT

General Conclusions of the Draft EPA Document

Using the 1986 Reports of both the National Research Council (NRC) and the U.S. Surgeon General as a starting point, the EPA document (U.S. EPA, 1990) seeks to extend the analysis of the apparent association between ETS and respiratory disease and pulmonary effects in children by reviewing relevant literature published since that time. The general conclusion of the document, as stated in its Executive Summary (p. 1-1), is as follows: ". . . exposure of young children to ETS from parental smoking, particularly during infancy, is associated with increased prevalence of acute lower-respiratory-tract infections (bronchitis and pneumonia), respiratory symptoms of irritation (cough, sputum, wheeze), and middle ear effusions (a sign of chronic middle ear disease). Passive smoking in early childhood is also associated with reduced lung function in children of mothers who smoke and with a small reduction in the child's rate of pulmonary growth and development. No conclusions are drawn regarding a potential association of parental smoking with the child's increased acute upper-respiratory-tract illnesses (colds and sore throats), an increased prevalence of asthma, or exacerbation of symptoms in asthmatic children."

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Comments on the EPA Report

As presented in Section II, our analysis arrives at a different conclusion. We feel that the conclusions of the draft EPA document are a reflection of the following characteristics: (1) incompleteness, (2) superficiality, (3) inaccuracies, and (4) lack of objectivity.

1. Incompleteness

Incompleteness is exemplified by the fact that numerous important articles that have been published since the NRC and Surgeon General's reports of 1986 have not been included in the EPA document.

2. Superficiality

Superficiality is apparent in several respects. Throughout the document, direct quotations were used without attribution. In addition, conceptual or seemingly factual statements were made that lacked appropriate citation. Certain concepts were alluded to while alternate explanations were not discussed or their complexity was not indicated. In other instances, several papers were mentioned to illustrate key points. However, there was little evidence that papers were reviewed critically, i.e., in light of their particular strengths and weaknesses.

3. Inaccuracies

Throughout the EPA report there are inaccuracies in either reporting or interpreting the findings of relevant studies; there are also critical omissions.

4. Lack of objectivity

The way in which this report treats the literature suggests that its objective from the outset was to establish an association between ETS exposure and both adverse respiratory health effects and impaired pulmonary function in offspring. This is evidenced by the following: 1) the dismissal on several occasions of statistical significance as a criterion for demonstrating an association, 2) deemphasis of critical confounding variables (such as recall bias and transfer of infection) or attempts to demonstrate that they have been addressed in select studies, when in reality they were not.

Throughout the draft of the EPA document there are numerous instances where the above four characteristics are exemplified. Specific examples, their location in the report, and our accompanying commentary are presented in the Appendix.

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VI. TABLES

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Table I. Parental Smoking and Respiratory Symptoms or Disease in Pre-School Children

Study	Significance[1]	Symptoms or illness (age, in yrs)
Cameron et al., 1969	-	respiratory illness (≤ 5)
Cameron & Robertson, 1973	+	respiratory illness (≤ 5)
Colley et al., 1974	+	bronchitis/pneumonia (≤ 1)
Ibid.	-	bronchitis/pneumonia (2-5)
Harlap and Davies, 1974	+,-	bronchitis/pneumonia, upper respiratory infections (≤ 1)
Leeder et al., 1976a	+	bronchitis/pneumonia (≤ 1)
Rantakallio, 1978	+	respiratory illness (< 5)
Sims et al., 1978	+	bronchiolitis (≤ 1)
Dutau et al., 1979	+	bronchitis and cough (< 12 mos)
Speizer et al., 1980	+	serious respiratory illness (< 2)
Dutau et al., 1981	+	respiratory infections (<6)
Fergusson et al., 1981	+	bronchitis/pneumonia and lower respiratory symptoms (≤ 1)
Ibid.	-	as above (2 & 3)
Pullan & Hey, 1982	+	respiratory syncytial virus infection (1)
Ekwo et al., 1983	+,+,-,-	respiratory (chest) illness, coughs with colds, wheeze, chest congestion and phlegm (<2)
Schenker et al., 1983	+	chest illness (< 2)
Hall et al., 1984	+,+	hospitalized for: respiratory syncytial virus infection, other respiratory disease (< 8)
Ware et al., 1984	+	respiratory illness (< 2)
Fergusson & Horwood, 1985	+,+	lower respiratory infection, lower respiratory symptoms (≤ 2)
Ferris et al., 1985	-,+,+	bronchitis, respiratory illness, wheeze (< 2)
Pedreira et al., 1985	+,+,-	bronchitis, tracheitis, bronchiolitis (1)
Tominaga & Itoh, 1985	+,+	asthmatic bronchitis, frequent colds (3)
Chen et al., 1986	+	hospitalization for respiratory illness (< 2)
McConnochie & Roghmann, 1986b	+	bronchiolitis (≤ 2)
Park & Kim, 1986	+	cough (< 5)
Strachan & Elton, 1986	+,-	wheeze, lower respiratory illness (< 5)
Bisgaard et al, 1987	+	wheeze (≤ 1)
Cogswell et al., 1987	+	wheeze in atopic and nonatopic children (5)
Fleming et al., 1987	+	upper respiratory tract infection (<5)

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Table I continued:

Study	Significance[1]	Symptoms or illness (age, in yrs)
Geller-Bernstein et al., 1987	+	wheezy bronchitis in atopic children (6 mos-5 yr)
Kershaw, 1987	+	asthma (≤ 5)
Ogston et al., 1987	+	respiratory illness (1)
Salzman et al., 1987	-	hospitalization for croup (< 5)
Stern et al., 1987, 1989	+	hospitalization for respiratory illness (< 2)
Taylor/Wadsworth, 1987	+,-	bronchitis, respiratory illness (5)
Toyoshima et al., 1987	+	wheeze or asthma (25-48 mos)
Chen et al., 1988	+,-,-,-	hospitalization for respiratory illness, asthma, whooping cough, sinusitis (≤ 18 mos)
Marks, 1988	+,-,-,-	cough or wheeze during exercise, recurrent wheeze, nocturnal cough, chest colds (4.5-5)
Charlton & Blair, 1989	+	absence from school[2]
Chen, 1989	+	hospitalization for respiratory illness in bottle-fed infants (≤ 18 mos)
Murray & Morrison, 1989	-	asthma (1-6)
Ostro, 1989	+	respiratory illness (< 6)
Harsten et al., 1990	-	respiratory tract infections (< 3)
Ross et al., 1990	-,+	upper respiratory tract infection, wheeze
Weitzman et al., 1990	+	asthma (≤ 5)

(Revised and updated from Witorsch, 1990)

[1] + = Significantly different from non-ETS exposed ($P \leq 0.05$); - = Not different from non-ETS exposed ($P > 0.05$).

[2] Includes all reasons for absence, not merely respiratory symptoms/disease, and is confounded by the fact that active smokers tend to be absent for reasons that are not health-related, and they are also considerably more likely to have one or both parents who smoke.

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